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EXAMINER	
ROYDS, LESLIE A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/615,275	DOLMANS ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *3,14,15 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4-13,16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12 July 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are presented for examination.

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/394,715, filed July 8, 2002. Applicant's Information Disclosure Statement (IDS) filed July 12, 2004 has been received and entered into the application. As reflected by the attached, completed copy of form PTO-1449 (one page total), the Examiner has considered the cited references. Applicant's response filed March 3, 2006 to the requirement for restriction/election dated September 28, 2005; the response filed March 5, 2006 in response to the notice of non-responsive amendment dated April 3, 2006; and the response filed June 9, 2006 in response to the notice of non-responsive amendment dated May 9, 2006 have each been received, considered and entered into the application.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group I (claims 5, 7 and 17-18), drawn to a method for administering photodynamic therapy (PDT) to a target tissue in a subject, wherein the target tissue is tumor tissue, and the election of pyrrole-derived macrocyclic compounds as recited in present claim 13 as the species of photosensitizer, wherein the first and second photosensitizer are the same compound, in the reply filed June 9, 2006 has been acknowledged by the Examiner. Claims 1-4, 6 and 8-16 are identified as linking claims and will be examined with the elected group.

Therefore, for the reasons above and those made of record at pages 2-6 of the previous Office Action dated September 28, 2005, the restriction requirement is deemed proper and is

made **FINAL**.

Claims 3, 14-15 and 19-22 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are 1-2, 4-13 and 16-18 and such claims are herein acted on the merits.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-13 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The present claims are directed to the use of pyrrole-derived macrocyclic compounds as the photosensitizing compound to be employed in the presently claimed method for administering photodynamic therapy to a target tissue of a subject.

Regarding the requirement for adequate written description, Applicant's attention is directed to the MPEP at §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by

structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Present claim 13 is directed to a method for administering photodynamic therapy as described in present claim 1, wherein the elected species of first and second photosensitizers are the same and are pyrrole-derived macrocyclic compounds. However, Applicant has failed to provide sufficient written description to support the use of "pyrrole-derived macrocyclic compounds". In fact, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical or functional properties that would provide adequate written description of the "pyrrole-derived macrocyclic compounds" that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention.

The present specification does not disclose or provide a limiting definition or any structural, chemical, physical or functional characteristics of these "pyrrole-derived macrocyclic analogs" such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by such a term. Although Applicant may assert that "pyrrole-derived macrocyclic compound" is a sufficiently limiting description of the structural nature of such compounds, the fact that the compounds are "pyrrole-derived" implies that the compounds may have some level of similarity to a pyrrole compound, but are not necessarily macrocyclic pyrrole compounds themselves. In other words, in the absence of any description of the degree of derivation of the "pyrrole-derived macrocyclic compound" relative to a standard or parent compound, Applicant has failed to provide adequate written description of those compounds intended to be included or excluded from the scope of such a term and still be considered a "pyrrole derivative" as intended by Applicant so as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, First Paragraph (Scope of Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-13 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of photodynamic therapy using the compound MV6401 (a methyl pyropheophorbide derivative with indium chelated in the center of the pyropheophorbide macrocycle) in mammary adenocarcinoma, does not reasonably provide

enablement for the administration of photodynamic therapy using any pyrrole-derived macrocyclic compound in any tumor tissue or the entire breadth of tumor types recited in present claim 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the unpredictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation. For the purposes of examination under 35 U.S.C. 112, first paragraph, the claims will be interpreted as reading upon the administration of photodynamic therapy for the purpose of treating tumor tissue as disclosed in the specification at page 6, second to last paragraph.

The presently claimed invention is directed to a method for administering photodynamic therapy (PDT) to a target tissue in a subject comprising administering an effective amount of a pyrrole-derived macrocyclic compound at a first time, administering an effective amount of a

pyrrole-derived macrocyclic compound at a second time after the first time and, thereafter, administering radiation to the target tissue in an amount and of a wavelength effective to activate the photosensitizing compound. The present claims are further directed to the treatment of tumor tissue and tumor vasculature, originating from a gastric, enteric, lung, breast, uterine, esophageal, ovarian, pancreatic, pharyngeal, sarcoma, hepatic, urinary bladder, upper jaw, bile duct, tongue, cerebral, skin, prostatic, parotid gland, malignant goiter, Hodgkin's disease, multiple myeloma, renal, leukemia, or malignant lymphocytoma cancer.

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the administration of photodynamic therapy using any pyrrole-derived macrocyclic compound to any tumor tissue would actually achieve the treatment of any tumor type in a subject. Based upon the state of the art with regard to cancer therapy and photodynamic therapy, as discussed below, the artisan would have only accepted that the administration of particular pyrrole-derived macrocyclic compounds to specific tumor tissue type(s) could treat the said specific tumor tissue type(s).

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to

make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe a method of administering photodynamic therapy to a target tissue of a subject, wherein the target tissue is tumor tissue and the photosensitizing compound is a pyrrole macrocyclic compound and the tumor tissue may be any one type selected from gastric, enteric, lung, breast, uterine, esophageal, ovarian, pancreatic, pharyngeal, sarcoma, hepatic, urinary bladder, upper jaw, bile duct, tongue, cerebral, skin, prostatic, parotid gland, malignant goiter, Hodgkin's disease, multiple myeloma, renal, leukemia, or malignant lymphocytoma. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed pyrrole-derived macrocyclic compound(s) and activating them by exposure to light that such a therapeutic objective of treating the tumor tissue could actually be achieved. However, in light of the fact that the specification fails to provide the skilled artisan with any direction or guidance as to what particular pyrrole-derived macrocyclic compounds could be employed in the method and how such compounds could be used for the treatment of tumor tissue, in general, or even the treatment of each of the types of tumor tissue presently claimed (please reference present claim 18), the present specification is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the use of the pyrrole-derived macrocyclic compounds, the specification fails to provide adequate written support or description of the compounds in terms of structural characteristics, chemical formula(s), name(s), or physical or functional properties such that one of ordinary skill in the art would have been reasonably apprised of the compounds that could be

employed in the method such that the artisan would have been imbued with a reasonable expectation of successfully executing the method using these photosensitizing compounds. However, in the absence of such descriptive characteristics of the compounds intended to be used within the method, and further, that Applicant has not provided even a non-limiting or exemplary definition of the compounds intended to fall within the scope of "pyrrole-derived macrocyclic compounds", nor provided any limiting definition as to the degree of derivation that a compound may have from a parent macrocyclic pyrrole compound and still be considered within the scope of the present invention, the specification lacks enabling disclosure of this aspect of the invention.

Applicant is reminded of MPEP §2164.08, which directs that all questions of enablement must be evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

It is clear that the exemplification of a single compound (MV6401, a methyl pyropheophorbide derivative with indium chelated in the center of the pyropheophorbide macrocycle) is not sufficient to then claim the much larger and highly varied genus of "pyrrole-derived macrocyclic compounds", particularly since the absence of a limiting definition of "derived" would leave such a genus of compounds open to subjective interpretation such that the

entire genus could conceivably read upon thousands, if not millions, of compounds, without any evidentiary or scientifically reasoned basis for extrapolating the results shown with this single compound to this larger genus of compounds with great variability in chemical, structural and functional properties. In the absence of such evidence or guidance by the specification, the skilled artisan would have no alternative recourse but the undue burden of experimentation in order to determine those compounds that could be used in the presently claimed method.

Regarding the treatment of any type of tumor tissue, the objective truth that any tumor tissue may be treated using the presently claimed method of administering photodynamic therapy using a pyrrole-derived macrocyclic compound is doubted because the state of the art expressly recognizes the obstacles associated with effective photodynamic therapy and the high degree of variation in the reactivity of different tumor types to a particular anticancer compound such that the use of a single agent, or even a single genus of structurally similar agents (i.e., "pyrrole-derived macrocyclic compounds"), in a method of administering photodynamic therapy to treat any tumor tissue would have been an outcome not reasonably expected by the skilled artisan.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and every type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Treatment of cancer using photodynamic therapy has its own art-recognized difficulties. Hsi et al. ("Photodynamic Therapy in the Treatment of Cancer: Current State of the Art", *Drugs*, 57(5); 1999:725-734) teaches, "PDT is a modality with significant potential as a cancer treatment. The recent development of new second-generation photosensitisers with decreased toxicity, improved selectivity and longer activation wavelengths will improve the efficacy of PDT and broaden its applications. The development of techniques for interstitial delivery of light will also make it possible to treat nonsuperficial tumors. Further investigation into light dosimetry will be necessary in both interstitial and superficial delivery systems. In addition, the changes in sensitizer concentration, oxygen tension and blood flow which occur during PDT must be defined to optimize conditions for maximal tumor cell killing effect." (see last paragraph at column 1 of page 732)

McCaughan Jr. corroborates these difficulties ("Photodynamic Therapy: A Review", *Drugs and Aging*, 15(1); 1999:49-68) by teaching, "Photodynamic therapy (PDT) of malignant tumors is a new technique for treating cancers...Different molecules and atoms absorb different wavelengths of energy. Since the light energy must be absorbed to start the photochemical reaction, the absorption spectrum of the photosensitiser determines the wavelength used to initiate the reaction. However, this can be qualified by the tissue the light has to travel through to get to the photosensitiser...Photodynamic therapy is an entirely new treatment modality and its development can be likened to that of the discovery of antibiotics. This is just the beginning, and its possible uses are only limited by the imagination." (see abstract at pages 49-50)

Sibata et al. ("Photodynamic Therapy in Oncology", *Expert. Opin. Pharmacother.*, 2001; 2(6):917-927) further teaches, "PDT produces an oxidative stress in cells and is a strong inducer

of apoptosis, which may account for the rapid cell killing response in treated tumors...Protocols that take advantage of the new understandings of these mechanisms are only now being developed. PDT has its shortcomings and several efforts have been undertaken to improve it. Photosensitisers of the second- and third-generation have been under investigation to improve the depth of light penetration into the tissue and, as a consequence, the depth of the treatment (a limitation for the first-generation photosensitiser)...Finally, there is progress being made in light measurements. Even though there may be enough photosensitiser in the tumor, the fluence delivered on the tumor surface may not be sufficient to optimally activate the PDT process throughout the target volume...A treatment-planning system, such as that for radiation therapy, is necessary to optimize PDT. There has been virtually no work in this area." (see paragraphs 2-5 of column 2 at page 923)

It is clear from the discussions presented in Hsi et al., McCaughan Jr. and Shibata et al. that the circumstances of effective photodynamic therapy are highly complex and must take into consideration many factors, since each photosensitiser will provide an apoptotic effect only under a unique set of circumstances. These include, but are not limited to, the toxicity of the compound, the ability of the compound to selective penetrate tumor cells, the concentration of the sensitizer, the wavelength, intensity and duration of light exposed to the compound and the ability of the light to penetrate the target tissue. Additionally, the art recognizes that the knowledge available to the skilled artisan is scant regarding the treatment of nonsuperficial tumors, due to the fact that penetration of tissue to deeply embedded lesions is an objective that is difficult, or even impossible, to achieve using photodynamic therapy as it is currently developed in the art. In other words, one of ordinary skill in the art would have been skeptical to

broadly apply the results demonstrated in the present specification using the compound MV6401 in mammary adenocarcinoma to the larger and more highly varied genus of "pyrrole-derived macrocyclic compounds" in general, tumors in general, or even any one of gastric, enteric, lung, breast, uterine, esophageal, ovarian, pancreatic, pharyngeal, sarcoma, hepatic, urinary bladder, upper jaw, bile duct, tongue, cerebral, skin, prostatic, parotid gland, malignant goiter, Hodgkin's disease, multiple myeloma, renal, leukemia, or malignant lymphocytoma, since the state of the art with regard to the use of photodynamic therapy is sufficiently underdeveloped and unpredictable such that the activity of one agent in treating a particular cancer would not necessarily translate into the same level of activity, or even any activity whatsoever, against a distinctly different compound in a distinctly different cancer. That is, the state of the art clearly dictates against the assertion that a single agent, in the present case, a pyrrole-derived macrocyclic compound, would have efficacy in treating any tumor that may exist in the art, or even the breadth of tumors specifically claimed, absent adequate direction or guidance as to how such an objective may be achieved with a reasonable expectation of success.

It is obvious from the discussion above that the state of the art with regard to the treatment of tumors using photodynamic therapy is highly unpredictable. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification requires more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326

(Fed. Cir. 2004).

Applicant provides an example solely directed towards the specific treatment of mammary adenocarcinoma using the compound MV6401. However, the instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed "pyrrole-derived macrocyclic compounds" for achieving the objective of treating tumor tissue in general, or even the breadth of tumor tissues presently claimed.

While a lack of a working embodiment cannot be a sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The fact that Applicant has exemplified the compound MV6401 in mammary adenocarcinoma does not address the high degree of variability in the art among the pyrrole-derived macrocyclic compounds claimed, the pathophysiological differences among different tumor types and their reactivity to anticancer therapies, and the fact that there is no art-accepted protocol for the use of photodynamic therapy using a single photosensitizing agent, or a single genus of photosensitizing agents, broadly against tumors in general. Applicant has also failed to provide any evidence, or describe any protocol, that addresses this variability in the art such that one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success in treating any tumor tissue, or even any one type of tumor tissue of those presently claimed, with a pyrrole-derived macrocyclic photosensitizing compound based on the direction provided in the instant specification.

Applicant's failure to rebut this presumption of unpredictability in the art by providing, by way of examples, guidance or persuasive scientific reasoning, as to why the working examples of the present disclosure would have been predictive of the same level of efficacy over the breadth of the subject matter presently claimed is clearly indicative of the need to resort to undue experimentation in order to execute the entire scope of the subject matter presently claimed. The basis for the rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation if necessary, it is undue*." (emphasis added) In the absence of such disclosure, it remains that the state of the art was such at the time of the invention that the high degree of unpredictability noted and recognized in the art with regard to photodynamic therapy for the treatment of cancer precludes the extrapolation of the results seen with the single agent MV6401 in mammary adenocarcinoma to the larger and much more highly varied genus of pyrrole-derived macrocyclic compounds in general and tumor tissue in general. In the absence of any direction or guidance presented by Applicant as to how such therapeutic objectives could be achieved without necessitating an undue level of experimentation, the present disclosure is viewed as lacking an enabling disclosure of the *entire scope* of the presently claimed subject matter.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors, establish, practicing the claimed invention in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the treatment of tumor tissue in general using the presently claimed method of administering photodynamic therapy using any pyrrole-derived macrocyclic compound could actually be achieved. In order to achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse by the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-9, 11-13 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present independent claim 1 is directed to a method for administering photodynamic therapy (PDT) to a target tissue in a subject, the method comprising: a) administering to the subject an effective amount of a first photosensitizer at a first time; b) administering to the subject an effective amount of a second photosensitizer at a second time after the first time; and, thereafter, c) administering to the target tissue radiation in an amount and of a wavelength

effective to activate the first and second photosensitizers, thereby administering PDT to the target tissue in the subject.

In particular, it is noted that Applicant has failed to define the objective of the method and what it is useful to do when executed as claimed. In other words, Applicant has not pointed out or distinctly claimed the intended purpose of the method, aside from the actual administration of the photodynamic therapy, for which performing the method will provide benefit. As a result, it is unclear from the claims as presently written for what Applicant intends to administer the photodynamic therapy.

For this reason, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, therefore, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dolmans et al. ("Photodynamic Therapy with MV6401 Induces Microvascular Damage in MCaIV Mammary Carcinoma", Abstract #588, *Proceedings of the American Association for Cancer Research*, March 2001) in view of Dolmans et al. ("Vascular Accumulation of a novel Photosensitizer, MV6401, Causes Selective Thrombosis in Tumor Vessels after Photodynamic Therapy", *Cancer Research*, April 2002), Hsi et al. ("Photodynamic Therapy in the Treatment of Cancer: Current State of the Art", *Drugs*, 1999; 57(5) :725-734) and Shibata et al. ("Photodynamic Therapy in Oncology", *Expert Opin. Pharmacother.*, 2001; 2(6):917-927).

Dolmans et al. (*Proceedings of the American Associated for Cancer Research*, 2001) teaches the administration of photodynamic therapy (PDT) using the photosensitizing compound MV6401 to immunocompetent C3H mice with MCaIV mammary carcinoma (lines 9-15) in an amount of 0.072 mg/kg or 0.036 mg/kg followed by 5 J/cm^2 of 664 nm light at 15 minutes following MV6401 administration (lines 12-16), which demonstrated a decrease in vascular density at 24 hours following PDT administration (lines 22-23).

Dolmans et al. (*Cancer Research*, 2002) is relied upon to show that the compound MV6401 is a macrocyclic compound containing pyrrole moieties and, thus, meets the limitation of a "pyrrole-derived macrocyclic compound", absent factual evidence to the contrary (see page 2152 at column 1).

Hsi et al. teaches that, "It appears that both direct cytotoxic activity and microvascular damage may contribute to the destruction of tumor tissue. The direct cytotoxic effect is the

result of incorporation of the photosensitisers into cellular membranes such as the plasma membrane. This damage is manifested by swelling, bleb formation, shedding of vesicles containing cytosolic enzymes and inhibition of membrane enzymes such as Na+, K+-ATPase...The vascular effect of PDT also contributes to varying degrees to tumor control. The mechanism of this effect vary with different photosensitisers although the end result of tumor hypoxia and anoxia is the same for all photosensitisers." (see paragraphs 2 and 5 at column 1 of page 727)

The primary reference to Dolmans et al. (*Proceedings of the AACR*, 2001) teaches a single administration of MV6401 compound at 15 minutes prior to irradiation with light, which is shown to permeate the tumor vasculature and decrease vascular density over the 24 hours following administration of PDT. This is confirmed by Dolmans et al. (*Cancer Research*, April 2002), who teaches that MV6401 is localized to the vascular compartment of the tumor after at least 15 minutes following administration, but further teaches that MV6401 is found to extravasate to the surrounding tumor tissue at later time points, such as 45 minutes to 4 hours (see paragraph 2 at column 2 of page 2152).

In light of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to maximize the efficacy of the photodynamic therapy disclosed by Dolmans et al. (*Proceedings of the AACR,* 2001) by targeting not only the vasculature of the tumor, but also the tumor size by enhancing the cytotoxic effects of the MV6401 compound, by administering two doses, one up to four hours prior to the application of light in order to allow time for the compound to penetrate the tumor tissue and enhance cytotoxicity of PDT and another within about 15 minutes prior to the application of light in order

to allow time for the compound to permeate the vasculature, but not long enough to extravasate to the tumor tissue. Such a person would have been motivated to do so in order to optimize the efficacy of the PDT application by targeting and eliminating both cell replication and the angiogenic process by which tumors are capable of sustaining themselves.

In further support of the use of multiple fractionated treatments, Hsi et al. teaches that multiple fractionated treatments were used with newer photosensitizing compounds to allow greater depth of tissue penetration with minimal skin phototoxicity (see abstract at page 725). Additionally, Shibata et al. teaches, "The main advantage of PDT is that the treatment can be repeated multiple times safely, without producing immunosuppressive and myelosuppressive effects and can be administered even after surgery, chemotherapy or radiotherapy." (see abstract at page 917)

Additionally, while Dolmans et al. (*Proceedings of the AACR*, 2001) teaches the use of 0.072 mg/kg or 0.036 mg/kg of the photosensitizing compound MV6401, the determination of the optimum dosage amounts and schedule of administration to treat the tumor tissue with the presently claimed photosensitizing agent would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage amounts and schedule of administration that would have actually been employed would have varied widely and, in the absence of evidence to

the contrary, the currently claimed specific dosage amounts and administration schedule are not seen to be inconsistent with that which would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Conclusion

Rejection of claims 1-2, 4-13 and 16-18 is proper.

Claims 3, 14-15 and 19-22 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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August 16, 2006

8/18/06
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